US 20210221826A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2021/0221826 A1**

Bradner et al. (43) **Pub. Date: Jul. 22, 2021**

(54) **BIVALENT BROMODOMAIN INHIBITORS AND USES THEREOF**

(71) Applicant: **Dana-Farber Cancer Institute, Inc.**, Boston, MA (US)

(72) Inventors: **James E. Bradner**, Weston, MA (US); **Jun Qi**, Sharon, MA (US); **Minoru Tanaka**, Boston, MA (US); **Justin M. Roberts**, Cambridge, MA (US)

(73) Assignee: **Dana-Farber Cancer Institute, Inc.**, Boston, MA (US)

(21) Appl. No.: **17/122,258**

(22) Filed: **Dec. 15, 2020**

Related U.S. Application Data

(62) Division of application No. 15/778,831, filed on May 24, 2018, now Pat. No. 10,913,752, filed as application No. PCT/US2016/063502 on Nov. 23, 2016.

(60) Provisional application No. 62/338,968, filed on May 19, 2016, provisional application No. 62/261,703, filed on Dec. 1, 2015, provisional application No. 62/259,797, filed on Nov. 25, 2015.

Publication Classification

(51) **Int. Cl.**

C07D 519/00	(2006.01)
A61K 31/551	(2006.01)
A61P 15/16	(2006.01)

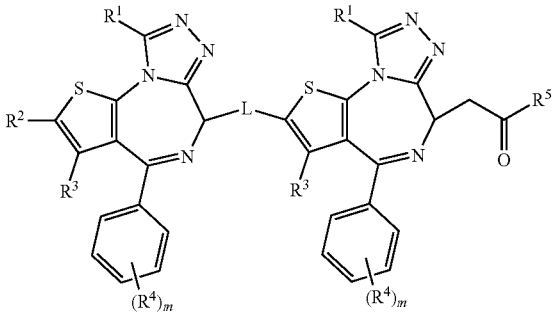
(52) **U.S. Cl.**

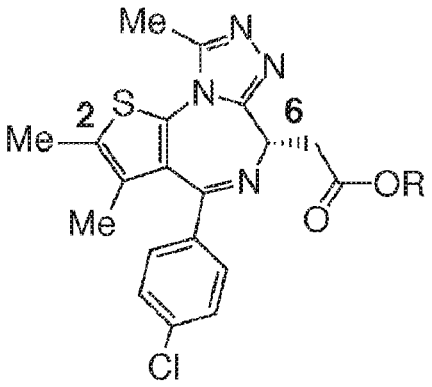
CPC ***C07D 519/00*** (2013.01); *Y02A 50/30* (2018.01); ***A61P 15/16*** (2018.01); ***A61K 31/551*** (2013.01)

(57) **ABSTRACT**

The present invention provides bivalent inhibitors of BET bromodomains, such as compounds of Formulae (I), (II), (III), (IV), (V), and (VI). Some bromodomain-containing proteins (e.g., BRD4) have a tandem bromodomain primary structure comprising more than one bromodomain binding site (e.g., BRD4 comprises BD1 and BD2). Bivalent inhibitors of BET bromodomains provided herein can target bromodomains through advantageous multivalent interactions, and can therefore can be to treat diseases or conditions associated with bromodomain-containing proteins. The present also provides pharmaceutical compositions and kits comprising the inventive compounds, as well as methods of using the inventive compounds.

(I)





JQ1: R = t-butyl
BRD4(1): IC_{50} = 21 nM
NMC797: IC_{50} = 69 nM
MV4;11: IC_{50} = 72 nM

MS417: R = Me
BRD4(1): IC_{50} = 13 nM
NMC797: IC_{50} = 18 nM
MV4;11: IC_{50} = 30 nM